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Craniofacial Structure in Diastrophic Dysplasia—A Cephalometric Study

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Diastrophic dysplasia (DTD) is a well characterized, recessively inherited osteochondrodysplasia. Forty-eight patients with DTD were studied for craniofacial characteristics. Of these patients, 58% had cleft palate. A cephalometric analysis based on lateral cephalograms was performed. We observed a short anterior cranial base, vertical nasal bones, short and posteriorly positioned upper and lower jaws, increased anterior facial height, increase in the sagittal length of the body of the cervical vertebrae, and an abnormal dens of the second cervical vertebra. DTDST, in which mutations responsible for the disease occur, is a gene that codes for a sulphate transporter membrane protein. The craniofacial anomalies in DTD most likely result from deficient development and growth of cartilaginous structures and are probably due to defective sulfation of the proteoglycans of the cartilage. Am. J. Med. Genet. 72:266–274, 1997. © 1997 Wiley-Liss, Inc.

KEY WORDS: diastrophic dysplasia; osteochondrodysplasia; cephalometric analysis

INTRODUCTION

Diastrophic dysplasia (DTD) comprises short-limbed short stature, generalized joint dysplasia, flexion limitation of the finger joints, hitchhiker thumbs, and metatarsus adductus deformity of the feet [Lamy and Maroteaux, 1960; Walker et al., 1972]. At least half of the patients have either isolated or submucous cleft palate or its microforms, which result in dental and phoniatric problems [Walker et al., 1972; Rintala et al., 1986; Karlstedt et al., 1996]. Facial anomalies include round face with a flattened bridge of the nose, small retrognathic mandible, and peculiar anomalies of the earlobes [Lamy and Maroteaux, 1960; Walker et al., 1972].

DTD is an autosomal recessive trait. According to case reports, it occurs with a low frequency in most populations, whereas in Finland there is a high prevalence–the gene carrier frequency being 1–2% [Kaitila, 1980]. The DTDST gene, in which mutations responsible for the disease occur, codes for a sulphate transporter membrane protein. Impaired function of this protein is thought to lead to undersulfation of proteoglycans in cartilage matrix. Three heterozygous mutations of the gene in five unrelated DTD patients have been detected [Hästbacka et al., 1994]. Recently, additional mutations found in the DTDST gene were reported to cause two additional chondrodysplasias: atelosteogenesis type II (AOII) [Hästbacka et al., 1996] and achondrogenesis type IB (ACG-IB) [Superti-Furga et al., 1996], both of them lethal disorders.

Earlier clinical studies on DTD mainly focused on the orthopedic problems of the joints and the spine. Except for the cleft palate, the craniofacial area was largely ignored. The aim of this study was to analyze the differences in the craniofacial area and upper cervical vertebrae in DTD patients compared to healthy controls.

MATERIALS AND METHODS

Patients

A number of patients diagnosed earlier at the Department of Clinical Genetics, Helsinki University Central Hospital were sent a letter of invitation describing the aims of the study. Of these patients, 53 (32 females and 21 males) participated in the study, their ages ranging from 1 to 44 years. Expression of the disease varied from moderate to quite severe; standing height of the patients ranged from −3 to −12 SD.

The study was approved by the Ethics Committee of the Institute of Dentistry, University of Helsinki.

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Methods

A clinical examination of the head and oral region was carried out at the Department of Pedodontics and Orthodontics, University of Helsinki, by one of the investigators (EK). Lateral cephalograms were taken at the Department of Dental Radiology, University of Helsinki. The patients were seated with their head positioned in a cephalostat and oriented to the Frankfort horizontal plane, with teeth in the intercuspal position. Lateral cephalograms were not taken from non-cooperative small children (n = 4), nor from one severely affected male. Altogether 48 lateral cephalograms were obtained (nF = 31, nM = 17). Of these patients, 28/48 (58%) had either isolated or submucous cleft palate. Corrective surgery had been performed on all isolated clefts but not on any of the submucous clefts.

A control group comprised patients from the Department of Pedodontics and Orthodontics, University of Helsinki. For each DTD patient, two controls were chosen of matching sex and age, normal occlusion, good facial balance, and no previous history of orthodontic treatment.

Altogether 77 landmarks were identified from the lateral cephalograms and traced on acetate tracing paper. Those of interest are presented in Figure 1. The definitions of these commonly used landmarks have been published earlier [Hellsing, 1991; Bhatia and Leighton, 1993]. The traced cephalograms were digitized with a computer-connected digitizer and 160 linear and angular measurements were calculated. Radiographic enlargement (10%) was corrected before the statistical analyses. The patients were divided into five age groups, presented in Table I. The groups were then divided into two subgroups: patients with and without cleft palate. Since only minor differences were found between the subgroups, they were pooled. For each group of patients and controls the arithmetic mean and the 95% confidence interval was calculated, separately for each measurement. Student's t-test was used for testing the significance of differences between DTD patients and the controls.

We compared our findings with studies on normal craniofacial growth and development and with studies on patients with isolated cleft palate, two hereditary chondrodysplasias, and three short stature syndromes.

Reliability

Thirty-four cephalograms were traced and digitized twice with a two-week interval in order to calculate errors in landmark identification. The error variance for each measurement was calculated from the formula $S_{(i)} = \sqrt{(\sum d^2/2N)}$, where d is the difference between the first and second tracing and N is the number of double tracings. Also, the difference between two digitations ($S_{(d)}$) from the same tracing was calculated for 15 cephalograms using the same formula, d being now the difference between the first and second digitation and N the number of double digitations. The range of error variance between two tracings was 0.39–1.13 mm for linear and 0.17–1.9 degrees for angular measurements, and between two digitations 0.18–0.50 mm and 0.23–1.49 degrees, respectively. This was considered acceptable when compared to other cephalometric studies.

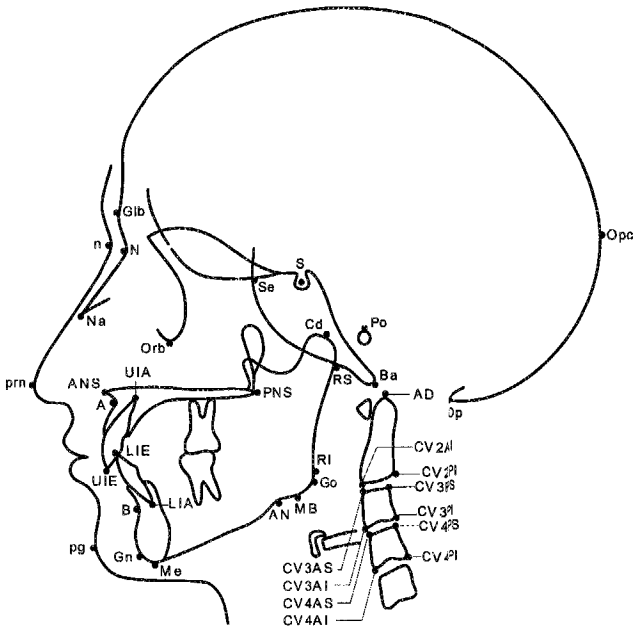

Fig. 1. The reference points of interest used in the cephalometric analyses. Abbreviations: S: sella; Se: sphenoethmoidal point; N: nasion; Na: nasal apex; Glb: glabella; Orb: orbitale; ANS: anterior nasal spine; PNS: posterior nasal spine; Ba: basion; Op: ophistion; Opc: ophistocranion; Po: porion; A: A-point; UIE: upper incisor edge; UIA: upper incisor apex; LIE: lower incisor edge; LIA: lower incisor apex; B: B-point; Gn: gnathion; Me: menton; Go: gonion; Cd: condylion; MB: mandibular base; RS: ramus superior; RI: ramus inferior; AN: antegonial notch; n: soft tissue nasion; prn: pronasale; pg: soft tissue pogonion; AD: apex dentis; CV2AI: cervical vertebra 2. anterior inferior; CV2PI: cervical vertebra 2. posterior inferior; CV3AS: cervical vertebra 3. anterior superior; CV3AI: cervical vertebra 3. anterior inferior; CV3PS: cervical vertebra 3. posterior superior; CV3PI: cervical vertebra 3. posterior inferior; CV4AS: cervical vertebra 4. anterior superior; CV4AI: cervical vertebra 4. anterior inferior; CV4PS: cervical vertebra 4. posterior superior; CV4PI: cervical vertebra 4. posterior inferior.

RESULTS

In Table II there are mean values, 95% confidence intervals (CI), and significance levels presented for the most interesting cephalometric measurements of the five groups of DTD patients and controls. For others, the significance levels are included in the text.

Cranial Base

The anterior cranial base (S-N) was short in DTD patients. The length of the posterior cranial base (S-Ba) did not differ from controls at a statistically significant

TABLE I. DTD Patients Divided Into Five Age Groups (patients with and without cleft palate are pooled)

Group	Age	Mean	N
1	4 < 7	5.3	6
2	7 < 13	9.9	8
3	13 < 20	17.9	10
4	20 < 30	25.5	12
5	30 < 45	35.4	12

TABLE II. Mean Values and 95% Confidence Intervals (CI) for the Cephalometric Measurements of the Most Interest, Calculated Separately for the Five Groups of DTD Patients and Controls (linear measurements in millimeters, angular in degrees)

		DTD		Controls		
Variable	Group	Mean	CI	Mean	CI	Sign.
Calvaria						
Gl-Opc	1	177.6	168.3–186.9	174.7	169.1–180.2	
	2	177.4	167.6–187.3	177.0	172.6–181.5	
	3	181.9	177.8–186.0	183.2	179.7–186.7	
	4	182.1	177.6–186.6	185.2	180.8–189.5	
	5	181.9	177.0–186.8	181.9	177.6–186.2	
Cranial base						
S-N	1	56.4	52.8–59.9	61.5	59.3–63.7	**
	2	61.2	58.7–63.8	64.1	62.6–65.6	*
	3	66.2	63.8–68.5	69.7	68.5–70.8	**
	4	65.5	62.3–68.7	68.8	67.3–70.3	*
	5	66.5	64.6–68.3	68.1	66.5–69.6	
S-Se	1	20.0	17.0–22.9	23.4	21.7–25.0	*
	2	20.3	19.2–21.4	24.2	22.9–25.6	***
	3	23.6	21.2–25.9	25.2	23.8–26.5	
	4	23.4	21.2–25.6	24.5	23.4–25.6	
	5	23.8	22.4–25.2	25.1	24.1–26.2	
S-Ba	1	38.0	35.4–40.6	35.5	33.3–37.7	
	2	40.8	39.0–42.7	39.2	38.0–40.5	
	3	42.6	39.9–45.2	45.1	43.4–46.8	
	4	43.0	41.4–44.5	44.4	42.8–46.1	
	5	42.7	40.2–45.2	43.9	42.0–45.8	
N-S-Ba	1	135.9	130.6–141.2	131.7	127.8–135.7	
	2	137.5	133.2–141.7	130.6	128.7–132.5	***
	3	132.6	130.2–135.0	130.0	127.3–132.6	
	4	133.0	130.7–135.3	131.0	127.6–134.4	
	5	132.5	129.3–135.6	130.6	128.6–132.7	
Ba-Op	1	33.2	30.8–35.7	33.5	30.3–36.6	
	2	36.9	34.1–39.7	35.3	33.0–37.5	
	3	39.8	37.2–42.4	38.4	36.9–39.9	
	4	37.9	36.4–39.3	38.1	36.1–40.2	
	5	39.2	36.7–41.6	38.1	36.9–39.4	
S-N-Na	1	93.3	89.7–96.8	104.4	100.5–108.3	***
	2	95.2	91.4–99.0	106.3	102.9–109.8	***
	3	107.4	102.3–112.6	111.4	107.9–115.0	
	4	107.6	102.8–112.5	114.0	110.9–117.1	*
	5	107.7	102.3–113.1	117.0	113.1–120.9	**
Maxilla						
ANS-PNS	1	42.8	40.7–44.9	44.2	42.4–46.0	
	2	45.8	43.3–48.2	47.4	46.0–48.9	
	3	48.8	46.2–51.5	53.6	52.1–55.1	**
	4	49.8	47.7–51.9	55.3	53.5–57.1	***
	5	50.3	48.5–52.1	55.7	54.0–57.3	***
ANS-S	1	63.9	60.6–67.2	72.1	69.3–74.8	***
	2	68.9	65.7–72.1	76.6	74.7–78.5	***
	3	76.6	72.6–80.7	83.8	81.7–85.9	**
	4	77.8	75.2–80.4	86.2	83.9–88.4	***
	5	77.9	75.7–80.1	85.6	83.6–87.6	***
ANS-Ba	1	78.8	73.7–83.8	85.0	81.9–88.1	*
	2	84.3	79.9–88.6	89.1	86.8–91.5	*
	3	89.3	84.6–93.9	97.5	95.0–100.1	**
	4	91.0	87.8–94.2	100.3	97.2–103.3	***
	5	91.0	87.2–94.8	99.6	97.2–102.0	***
S-N-A	1	75.1	71.6–78.7	81.2	78.9–83.5	**
	2	73.4	70.4–76.3	81.7	80.3–83.2	***
	3	75.0	72.1–77.9	80.9	78.3–83.5	**
	4	77.6	74.7–80.5	83.4	81.7–85.2	***
	5	77.0	74.5–79.4	83.7	81.6–85.8	***
S/N-ANS/PNS	1	7.3	2.8–11.8	4.8	2.7–7.0	
	2	7.6	4.2–11.0	6.3	5.5–7.2	
	3	8.0	6.3–9.7	6.0	4.3–7.8	
	4	6.7	4.1–9.2	6.6	5.3–8.0	
	5	4.6	3.3–5.9	7.0	5.5–8.5	*
Mandible						
Cd-Gn	1	84.1	78.2–90.1	90.3	86.1–94.4	
	2	93.9	86.5–101.4	99.9	96.0–103.7	
	3	108.6	103.1–114.0	113.1	110.4–115.7	

TABLE II. Continued

Variable	Group	DTD Mean	DTD CI	Controls Mean	Controls CI	Sign.
	4	105.5	101.1–110.0	115.3	111.0–119.5	**
	5	108.3	103.3–113.3	114.1	110.0–118.2	
Cd-Go	1	41.4	37.7–45.1	42.5	39.5–45.6	
	2	43.7	40.3–47.0	45.8	43.8–47.9	
	3	52.6	49.6–55.6	54.9	51.2–58.6	
	4	52.2	49.4–54.9	56.5	54.1–59.0	*
	5	51.2	47.6–54.8	55.8	52.5–59.1	
Go-B	1	50.4	46.6–54.2	57.0	54.7–59.3	**
	2	57.0	52.2–61.7	64.7	62.2–67.3	**
	3	63.7	59.4–67.9	69.8	67.7–72.0	**
	4	62.7	59.1–66.3	71.1	68.4–73.8	***
	5	64.7	61.1–68.4	69.3	66.6–72.0	*
Cd-Go-Me	1	132.6	127.2–138.0	129.7	126.0–133.5	
	2	131.5	127.6–135.5	125.3	123.5–127.2	**
	3	128.2	124.5–131.9	125.1	121.6–128.6	
	4	126.7	123.4–129.9	123.6	120.9–126.2	
	5	126.1	122.5–129.7	124.6	122.3–126.9	
N-S-Gn	1	75.2	71.4–79.1	63.6	61.4–65.8	***
	2	75.6	72.6–78.5	64.0	62.8–65.1	***
	3	72.7	69.4–75.9	66.5	63.9–69.2	**
	4	72.3	68.9–75.7	65.1	63.4–66.8	***
	5	72.8	69.9–75.7	64.4	62.7–66.2	***
S/N-MB/Me	1	42.5	36.1–49.0	32.2	29.1–35.4	**
	2	43.7	40.5–47.0	30.9	29.3–32.4	***
	3	40.6	36.9–44.3	32.0	27.9–36.1	**
	4	37.4	33.7–41.1	29.1	26.6–31.5	***
	5	38.3	34.3–42.4	28.7	26.0–31.4	***
S-Gn	1	90.5	85.7–95.3	96.4	92.2–100.6	
	2	100.4	93.5–107.4	105.3	101.8–108.8	
	3	115.4	110.3–120.5	119.2	116.6–121.9	
	4	114.6	109.8–119.5	120.7	116.5–124.9	
	5	117.2	112.9–121.4	119.8	116.3–123.3	
Ba-Gn	1	79.2	72.6–85.8	89.4	86.1–92.8	**
	2	88.9	81.8–96.1	96.6	93.7–99.6	*
	3	101.1	96.3–105.9	107.2	104.7–109.6	*
	4	100.8	95.2–106.5	110.2	106.0–114.4	**
	5	103.3	97.9–108.6	109.7	106.3–113.1	*
S-N-B	1	70.4	66.2–74.5	78.8	76.1–81.5	***
	2	69.5	67.6–71.4	79.2	78.4–80.0	***
	3	73.3	70.4–76.2	78.5	76.7–80.4	**
	4	74.0	71.1–77.0	79.8	77.9–81.6	***
	5	73.3	70.5–76.2	80.4	78.3–82.5	***
AN from MB/Me	1	2.5	1.6–3.4	1.4	1.1–1.7	**
	2	2.6	1.9–3.2	0.8	0.5–1.1	***
	3	2.9	2.2–3.6	1.1	0.5–1.8	***
	4	2.3	1.7–2.8	0.8	0.5–1.1	***
	5	2.2	1.8–2.7	0.9	0.4–1.4	***
Jaw relations						
ANS/PNS-MB/Me	1	35.2	32.4–38.1	27.4	24.3–30.5	**
	2	36.1	32.0–40.3	24.6	22.9–26.3	***
	3	32.6	29.2–35.9	25.7	22.2–29.1	**
	4	30.7	27.2–34.2	22.4	20.1–24.8	***
	5	33.5	29.1–38.0	21.7	19.4–24.1	***
A-N-B	1	4.8	3.5–6.1	2.5	1.5–3.4	**
	2	3.9	1.6–6.2	2.7	1.8–3.5	
	3	2.3	1.0–3.6	2.6	1.4–3.8	
	4	3.6	1.9–5.3	3.8	2.6–4.9	
	5	3.8	2.2–5.5	3.3	2.2–4.5	
Facial height						
N-ANS	1	39.8	36.1–43.5	39.2	36.3–42.0	
	2	45.5	41.3–49.7	44.5	42.7–46.3	
	3	50.0	48.2–51.7	49.8	48.1–51.6	
	4	50.0	47.6–52.3	50.5	49.1–52.0	
	5	49.7	48.0–51.4	49.6	48.2–51.1	
ANS-Me	1	58.1	55.7–60.5	53.8	52.1–55.6	**
	2	62.6	59.3–66.0	56.5	54.6–58.5	**
	3	68.2	64.6–71.9	67.0	64.3–69.8	
	4	67.6	64.1–71.2	66.3	63.4–69.2	
	5	70.7	67.9–73.5	65.3	63.2–67.4	**

(Continued)

TABLE II. Continued

Variable	Group	DTD Mean	DTD Cl	Controls Mean	Controls Cl N-Me	Sign.
N-Me	1	95.7	90.0–101.4	91.2	87.0–95.3	
	2	106.5	99.9–113.1	99.4	95.9–102.9	*
	3	116.9	112.3–121.6	115.2	111.2–119.2	
	4	115.8	110.6–121.0	114.3	110.6–118.0	
	5	118.7	115.2–122.2	112.6	109.8–115.4	**
S-PNS	1	34.8	31.3–38.3	39.1	37.0–41.1	*
	2	39.4	35.8–42.9	42.1	40.9–43.3	*
	3	43.8	42.1–45.5	46.3	45.0–47.6	*
	4	45.2	43.2–47.2	46.6	44.9–48.4	
	5	46.4	44.3–48.4	45.2	43.7–46.8	
PNS-Go	1	31.8	31.3–32.2	32.3	30.2–34.3	
	2	33.1	30.7–35.5	35.4	33.9–36.8	
	3	38.2	34.9–41.4	40.3	37.8–42.7	
	4	38.7	35.6–41.7	42.5	41.1–43.8	*
	5	38.5	35.1–41.8	41.6	39.3–43.8	
S-Go	1	56.5	53.6–59.5	57.2	53.4–61.0	
	2	60.5	56.2–64.8	62.0	59.9–64.0	
	3	69.1	65.6–72.5	72.6	69.0–76.2	
	4	71.4	67.7–75.2	74.8	71.9–77.6	
	5	70.8	66.7–75.0	74.0	70.8–77.2	
Cervical column						
CV2AI-CV2PI	1	12.3	10.8–13.9	10.7	9.9–11.5	*
	2	14.9	13.3–16.5	12.3	11.8–12.9	***
	3	17.7	16.0–19.3	14.1	13.3–14.9	***
	4	17.6	16.2–19.1	13.7	13.0–14.3	***
	5	18.4	16.8–20.1	14.3	13.5–15.1	***
CV3AI-CV3PI	1	12.3	11.1–13.6	11.2	9.5–12.8	
	2	15.7	14.2–17.1	12.1	11.5–12.6	***
	3	19.7	18.0–21.4	14.1	13.1–15.0	***
	4	19.5	18.0–20.9	14.1	13.3–14.8	***
	5	20.5	18.9–22.0	14.4	13.4–15.3	***
CV3AS-CV3AI	1	4.6	3.0–6.2	4.9	4.0–5.8	
	2	7.2	5.6–8.8	6.5	5.9–7.1	
	3	12.2	10.9–13.4	12.1	10.5–13.6	
	4	12.6	11.4–13.9	12.8	12.2–13.4	
	5	13.2	12.0–14.4	13.1	12.3–14.0	
CV4AI-CV4PI†	3	18.7	17.2–20.1	14.0	12.5–15.4	***
	4	19.9	18.1–21.6	14.7	13.4–15.9	***
	5	20.3	17.6–23.1	14.7	13.6–15.8	***
CV4AS-CV4AI†	3	11.4	10.2–12.6	11.7	9.4–14.0	
	4	11.5	10.3–12.6	12.4	11.6–13.2	
	5	12.1	10.2–14.1	12.7	11.8–13.6	

*$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.
†Lower cervical column is not visible in the younger age groups because of the thyroid shield of the lead apron.

level. Neither did the sagittal length of the foramen magnum (Ba-Op). The cranial base angle (N-S-Ba) was slightly increased compared to controls. The angle between the nasal bones and anterior cranial base (S-N-Na) was small.

Maxilla

The maxilla (ANS-PNS) was short compared to controls. It was also situated more posteriorly in respect to the cranial base; the distance from anterior nasal spine to both sella and basion were short compared to controls. Also, the S-N-A angle was small. The upper anterior alveolar height (UIE from ANS/PNS) exceeded that of controls in every age group and the difference was statistically significant in groups 1, 2, and 5 ($P < 0.05$, < 0.001, < 0.01, respectively).

Mandible

The mandible was short and rotated posteriorly. The mandibular body (Go-B) was especially short. The gonial angle (Cd-Go-Me) was increased, and the significantly larger N-S-Gn and S/N-MB/Me angles indicated backward rotation. The mandible was also positioned more posteriorly with respect to the cranial base; the distances from gnathion to both sella and especially basion were short and the S-N-B angle was small compared to controls. The angle between anterior cranial base and ramus line (S/N-RS/RI) was constant in all patients groups and did not differ from controls. The lower anterior alveolar height (LIE from MB/Me) exceeded that of controls, but the difference was at a statistically significant level only in groups 2 and 5 ($P < 0.05$). The antegonial notch (AN from MB/Me) was more pronounced in DTD patients.

Jaw Relations

Relations of the jaws in respect to each other did not differ from controls (A-N-B, UIE/UIA-LIE/LIA). Only the angle between palatal and mandibular planes (ANS/PNS-MB/Me) was increased in DTD patients.

Facial Height

The lower anterior facial height (ANS-Me) exceeded that of controls, resulting in an increased total anterior facial height (N-Me). The total posterior facial height (S-Go) did not differ from controls.

Soft Tissues

Facial convexity with nose (n-prn-pg) and without nose (n-sn-pg) did not differ from controls (data not shown).

Cervical Column

In groups 1 and 2, only the first three cervical vertebrae were measurable in lateral cephalograms, the others being covered by the thyroid shield of the lead apron. In groups 3–5 the fourth was also measurable. The lower length of the body of the second cervical vertebra (CV2AI-CV2PI) exceeded the value of controls in all groups, the difference being statistically significant. The same was observed in the third cervical vertebra in all groups except in group 1 and in the fourth cervical vertebra in all measured groups.

The morphology of the dens of the second cervical vertebra was distinct; the top third bending backwards with a bulky and triangular tip. The distance from the tip of the dens to the mesial border of the foramen magnum (AD-Ba) was longer than in controls in groups 2–5 (group 2, P n.s., group 3, $P < 0.05$, groups 4 and 5, $P < 0.001$).

Lateral cephalograms of four DTD patients with characteristic craniofacial features are presented in Figure 2.

DISCUSSION

In a large sample of DTD patients, we were able to demonstrate several craniofacial abnormalities: short anterior cranial base, vertical nasal bones, short and retrognathic upper and lower jaws, posteriorly rotated mandible, increased anterior face height, and increased sagittal length of the vertebral bodies in the upper cervical vertebra with an abnormal dens.

Craniofacial bones are derived from components of different origin. The first ossification centers at the craniofacial area appear at the 6th and 7th week i.u. at the intramembranously developing mandibular and maxillary bones, followed by centers at the adjacent facial and calvarial bones. Also, the earlier formed chondrocranium starts to ossify. Ossification centers expand and fuse to form bones that in the cranial base are partly endochondral and partly intramembranous in origin. Individual bones are separated by sutures and synchondroses, which contribute to growth by apposition of bone at their sites. The mandibular condyle appears at the 10th week i.u. as a secondary cartilage at the ramus of the intramembranously ossifying mandible [Sperber, 1989]. It acts as a growth region for the mandible and as an articular cartilage and thus differs in structure and function from the growth plates of long bones [Koski and Rönning, 1971]. Growth of the craniofacial area continues as a combination of bone remodelling, apposition of bone at sutures and synchondroses, condylar growth, and transposition and displacement of enlarged and remodelled bones [Sperber, 1989].

Calvaria

The length of the calvaria was not affected in DTD patients, indicating that sutural growth and remodelling of calvarial bones is undisturbed. In ACH, an enlarged calvaria is reported and considered to result from increased brain size [Cohen et al., 1985]. Calvaria of normal size was found in CHH [Rönning et al., 1978], and in Mulibrey nanism [Myllärniemi et al., 1978], Silver-Russell growth failure [Kotilainen et al., 1995], and Rubinstein-Taybi syndrome [Hennekam et al., 1991], and in cleft palate patients [Dahl et al., 1982].

Cranial Base

The anterior cranial base length from nasion to sella was short in DTD patients, and the shortness was most pronounced in the anterior sphenoidal length. Since cranial base is preformed in cartilage, this was not surprising. One would also expect the posterior cranial base length from sella to basion to be short compared to controls, yet that was not observed in the present study.

Anterior cranial base length includes frontal bone, cribriform plate, and anterior part of the sphenoid bone length in midsagittal plane. The two latter are endochondral in origin. Postnatally, the growth of the anterior cranial base length depends on growth in three suture sites: fronto-ethmoidal, sphenofrontal, and spheno-ethmoidal sutures, and ceases after the age of 7 years [Melsen, 1974; Sperber, 1989]. It seems that growth in the anterior cranial base was deficient and delayed in DTD patients. Also, the cartilaginous templates of the ethmoid and anterior sphenoid bones might have originally been small.

The posterior body of the sphenoid and the basioccipital bone constitute together the posterior cranial base, both being endochondral in origin. The growth of the posterior cranial base results from both endochondral bone formation at the spheno-occipital synchondrosis, acting as a bipolar growth plate, and remodelling resorption at the cranial side of clivus, and apposition at the pharyngeal side and anterior border of the foramen magnum. Normally, the closure of spheno-occipital synchondrosis is completed around age 13 in girls and 14–15 in boys [Ingervall and Thilander, 1972; Melsen, 1974]. Surprisingly, the distance from sella to basion was longer in the two youngest groups of DTD patients compared to controls. A possible explanation for this could be that the posterior cranial base structures are capable of compensative growth in order to provide sufficient cranial base support for the brain. Timing of the complete closure of the synchondrosis did not differ from controls.

In both ACH and CHH, normal anterior but short posterior cranial base length has been reported, although in ACH the short cribriform plate was found to be compensated by increased length of the anterior

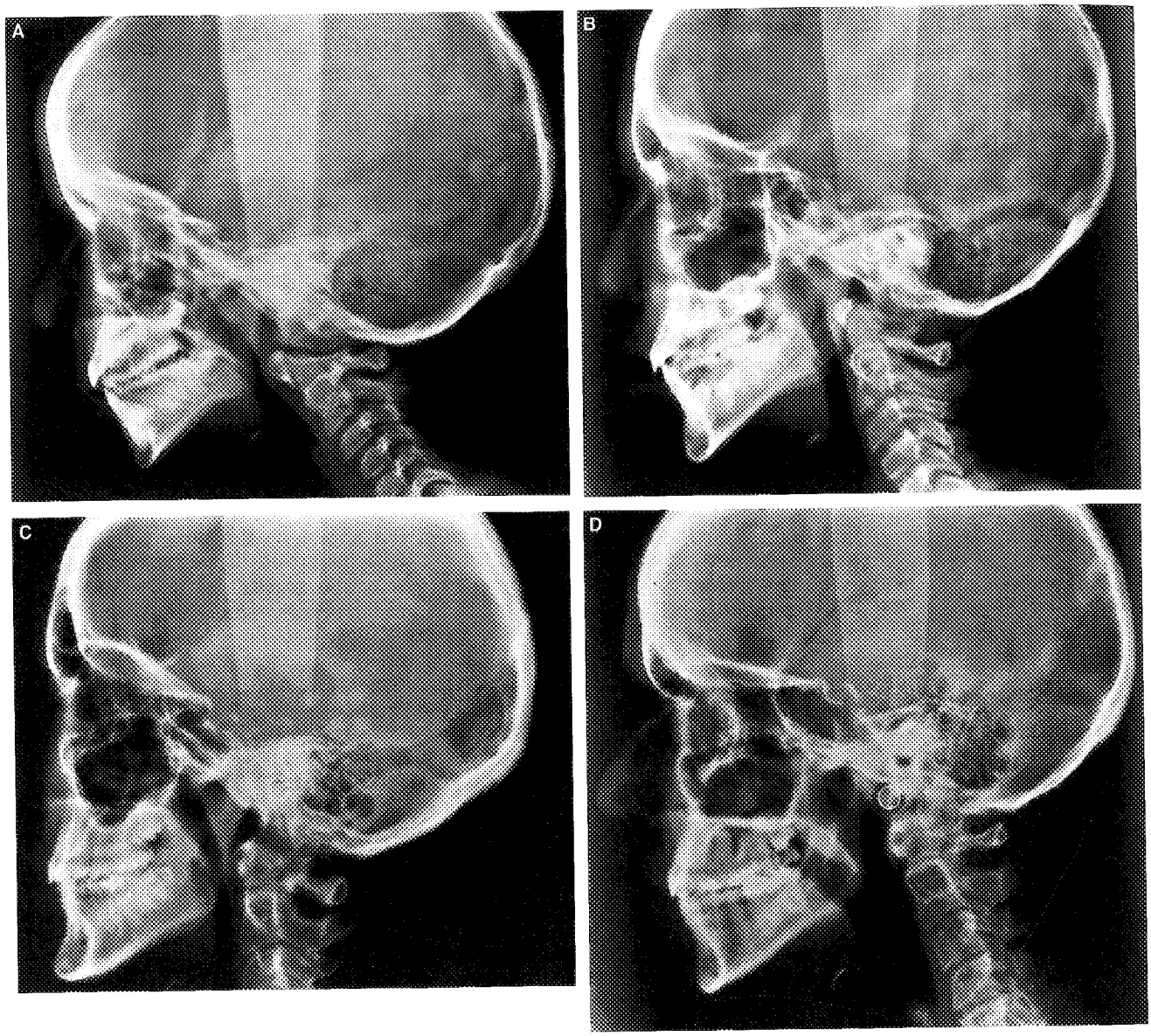

Fig. 2. Lateral cephalograms of four DTD patients. (**A**) 6-year-old boy, (**B**) 10-year-old girl with submucous cleft palate, (**C**) 17-year-old girl with cleft palate, and (**D**) 29-year-old woman.

sphenoid bone [Rönning et al., 1978; Cohen et al., 1985]. As for the three proportionate short stature syndromes, both the anterior and posterior cranial bases have been found to be short [Myllärniemi et al., 1978; Hennekam et al., 1991; Kotilainen et al., 1995].

Short cranial base was also reported in association with cleft palate. The anterior length has been found to be short already at an early age, and later growth of the posterior cranial base has been deficient. No difference has been established between operated and non-operated patients [Dahl, 1970; Bishara, 1973; Dahl et al., 1982].

The cranial base angle was slightly increased in DTD patients compared to controls. However, wide variation has been reported in population studies [Bhatia and Leighton, 1993]. In ACH, the cranial base angle is acute. This is thought to result from increased brain size and closure of the spheno-occipital synchondrosis earlier than normal [Cohen et al., 1985]. Large cranial base angle was reported in CHH [Rönning et al., 1978]. Different findings were published on the cranial base angle in patients with cleft palate, but most authors agree on normal flexure [Dahl, 1970; Bishara, 1973; Dahl et al., 1982].

The midsagittal length of the foramen magnum did not differ from that of controls. This was surprising, since it is surrounded by endochondrally ossifying bones and several synchondroses at the prenatal and early postnatal age. During normal growth, bone apposition at the anterior and resorption at the posterior margin of the foramen magnum maintains the space for the spinal cord. The normal size of the foramen

magnum indicates that bone remodelling at the cranial base is not affected in DTD. Both in ACH and CHH, a small foramen magnum has been reported [Rönning et al., 1978; Cohen et al., 1985], as well as in Silver-Russell syndrome [Kotilainen et al., 1995]. In Mulibrey nanism the size of the foramen magnum was not found to be affected [Myllärniemi et al., 1978].

The nasal bones were vertical but of normal length in DTD patients. The bones are intramembranous in origin but develop in close relation to the cartilaginous nasal septum [Sperber, 1989; Sandikcioglu et al., 1994]. A vertical orientation thus probably results from hypoplastic nasal septum in DTD patients. A similar finding has been reported in ACH [Cohen et al., 1985] and Mulibrey nanism [Myllärniemi et al., 1978]. However, the orientation was normal in patients with cleft palate [Dahl et al., 1982].

Maxilla and Mandible

Both jaws were found to be short and retrognathic in DTD patients, but the intermaxillary relation was normal. Short maxillary length is probably related to hypoplastic growth of the anterior cranial base and the nasal capsule: when displacement of the maxilla is reduced, remodelling at the posterior border (apposition) is reduced. The observed decrease of the angle between anterior cranial base and the palatal plane with age probably also results from the lack of normal forward- and downward-directed growth of the maxilla. The increased anterior upper alveolar height compared to controls results from dentoalveolar compensation to the high position of the maxilla [Björk and Skieller, 1972].

In the mandible, the shortness of the ramus was less marked than that of the mandibular body. These might indicate a deficient Meckel's cartilage, around which the mandibular bones start to ossify, and somewhat reduced condylar growth.

The growth direction of the mandible in DTD patients was downward and backward. Björk and Skieller found in their study of craniofacial growth assessed with implants that forward rotation was a general feature of normal facial growth and development. They also found that backward rotation of the mandible resulted in increased anterior lower face height, relatively low posterior face height, and compensatory eruption of lower incisors. Incomplete dentoalveolar compensation often manifested itself as anterior open bite and crowding [Björk and Skieller, 1972]. All these phenomena were observed in the present group of DTD patients, the latter two reported in our previous paper [Karlstedt et al., 1996]. If teeth and the skeletal components of the mandible are located posteriorly, the angle between anterior cranial base and mandibular plane is found to be high [Isaacson et al., 1971]. We observed the same in DTD patients.

The mean value for the angle between anterior cranial base and mandibular ramus line was constant through patient groups, indicating that remodelling existed in the gonial region [Björk and Skieller, 1972].

In ACH, Cohen et al. [1985] reported short and somewhat retruded maxilla and anteriorly positioned mandible due to acute cranial base angle. Maxilla and mandible of normal size are found in CHH [Rönning et al., 1978]. All three proportionate short stature syndromes are associated with short maxilla and mandible [Myllärniemi et al., 1978; Hennekam et al., 1991; Kotilainen et al., 1995].

Short and retrognathic maxilla and mandible are also associated with cleft palate, and their growth does not seem to be affected by surgery [Dahl, 1970; Bishara, 1973; Dahl et al., 1982; da Silva et al., 1992].

Cervical Column

The multiple problems of the spine in DTD patients were studied earlier; scoliosis, cervical kyphosis, and spina bifida are often present. Also, hypoplastic cervical vertebral bodies and block fusion have been reported [Herring, 1978; Bethem et al., 1980; Poussa et al., 1991]. The malformed and large dens observed in this study was also reported earlier [Poussa et al., 1991]. In the present study, no attempt was made to diagnose cervical kyphosis and spina bifida because of restrictions in the radiological methods used.

Sagittal length of the cervical vertebral bodies 2–4 was long in DTD patients compared to controls, but the height did not seem to be affected. In half of the patients, the shape and outlining of the vertebral bodies were obscure. Also, the lower border seemed to lack the concave form observed in the controls (Fig. 2b,d). The vertebral bodies are preformed in cartilage and growth takes place by endochondral ossification through proximal and distal epiphyseal plates as does the growth in the metaphyses of the long bones [Bick and Copel, 1950]. Since tubular bones are short in DTD, reduced height of the vertebral bodies would be expected. Yet this was not observed in the upper cervical vertebra.

In ACH, the trunk length was observed to be nearly normal. The authors speculated that the numerous growth centers in the vertebral column would allow adequate growth to take place [Cohen et al., 1985]. This could be the explanation also in DTD. Different types of cervical vertebral anomalies are associated with cleft palate. Prevalences from 9% up to 45% have been reported [Ross and Lindsay, 1965; Sandham, 1986; Horswell, 1991; Hoenig and Schoener, 1992]. Also, shortened cervical spine has been found [Smahel and Skvarilova, 1993].

During the past two years the molecular bases of a number of chondrodysplasias were detected. Of these conditions, ACH, thanatophoric dysplasia, and hypochondroplasia in which developmental abnormalities in the chondrocranium are present were found to be due to mutations in the FGFR3 gene [Horton, 1995]. It is of particular interest that mutations in the FGFR1 and FGFR2 result in other types of human cranial disorders, such as Apert, Crouzon, Pfeiffer, and Jackson-Weiss syndromes. Phenotypically these syndromes result from asynchronous early craniosynostoses, and as such are disorders of the flat bones of the skull [Muenke and Schell, 1995]. None of the conditions above are usually associated with cleft palate. Instead, the chondrodysplasias due to mutations in the collagen type II gene (COL2A1) often present with cleft palate

[Spranger et al., 1994]. The genotype-phenotype correlations have turned out to be difficult and, thus, the pathogenesis of the craniofacial anomalies, that of the cleft palate in particular, still remains to be resolved.

The gene for DTD, which resides on 5q, encodes a sulphate transporter membrane protein. Impaired function of its product is likely to lead to undersulfation of proteoglycans in cartilage matrix [Hästbacka et al., 1994]. Histological and histochemical studies on the cartilage matrix of DTD patients have demonstrated several abnormalities. Collagen fibrils are short and increased in diameter and form irregular fibril aggregates [Horton et al., 1979; Shapiro, 1992; Diab et al., 1994]. Diab et al. [1994] reported an electrophoretic abnormality in type IX collagen, which is thought to function as a regulator of type II collagen organization and function. Bailey et al. [1995] found abnormal collagen cross-linking in cartilage. The mechanisms between the gene defect and these anomalies are still unknown. Whether other tissues are affected is also unclear. However, indications of that are the observed alterations of tendons and joint capsules [Walker et al., 1972] and the reduced tooth size [Karlstedt et al., 1996].

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